REMARKS

Reconsideration of the outstanding Office Action is respectfully solicited.

The U.S. PTO Examiner is alerted to the submission of an INFORMATION DISCLOSURE STATEMENT (concurrently filed). The items noted on the 1449 are items which were located to address the Examiner's rejections and are used in the traversal below. No fee is believed to be due. However, should the US PTO consider otherwise, the US PTO is authorized to charge the requisite fee to Deposit Account 22-0261.

Applicants respectfully traverse the rejections of the claims over Erices *et al.* (*Br. J Hematol*, 109:235-242; 2000), Nishikawa *et al.* (US. Patent Application Publication No.: 2004/0235160; effective filing date: Aug. 7, 2002), and Petaja *et al.* (*J. Clin. Invest.* 99:2655-2663; 1997).

The subject of claim 1 is a method of isolating and culturing **mesenchymal stem** cells from **umbilical cord blood,** comprising the steps of: adding an anti-coagulant to umbilical cord blood having a volume of more than 45 ml per unit, which is obtained within 24 hours after parturition; diluting the resulting mixture of the anti-coagulant and umbilical cord blood with an αMEM (alpha-minimum essential medium), followed by centrifugation to harvest monocytes; and subjecting the obtained monocytes into suspension culture in the αMEM containing Stem Cell Factor, GM-CSF (granulocyte-macrophage colony-stimulating factor), G-CSF (granulocyte colony-stimulating factor), IL-3 (interleukin-3) and IL-6 (interleukin-6)"

The method includes a reproducible method of isolating and culturing mesenchymal stem calls **from umbilical cord blood**, thereby making it possible to secure primitive mesenchymal stem cells and improve the success rate of cell culture up to about 90%, while that of the conventional method is less than 10%.

In Applicant's view, the analysis in the U.S. PTO rejection does not appear to establish the differences between the subject matter claimed and the information in the applied references; this determination of differences is one of the elements of the *Graham v. John Deere* investigation. In Applicant's view, the Graham inquiry is still U.S. PTO

policy with respect to the analysis the PTO must undertake in reaching any conclusion under 35 U.S.C. 103(a). It is the objective initial factual inquiry. Applicants note the following differences between the claimed invention and the cited references, Erices *et al.* (*Br. J Hematol*, 109:235-242; 2000), Nishikawa *et al.* (US. Patent Application Publication No.: 2004/0235160; effective filing date: Aug. 7, 2002), and Petaja *et al.* (*J. Clin. Invest.* 99:2655-2663; 1997).

Erices *et al.* (*Br. J Hematol.* 109:235-242; 2000) relates to mesenchymal **progenitor** cells in human umbilical cord blood. By comparison, a characteristic feature of the rejected claims is that **mesenchymal stem cells** are isolated and cultured from **umbilical cord blood**, wherein the umbilical cord blood is diluted with αMEM, followed by centrifugation so as to harvest monocytes, which are then cultured in αMEM including Stem Cell Factor, GM-CSF, G-CSF, IL-3 and IL-6.

In Erices *et al.*, cord blood is diluted with M-199 and the diluted cord blood cells are separated into a low-density fraction to obtain mononuclear cells, which are suspended into culture medium comprising αMEM, fetal bovine serum and gentamycin sulfate.

Those are some of the differences between Erices et al and the rejected claims. Thus the method used by Erices *et al.* is different from the subject invention with respect to the dilution medium and with respect to the components of culture medium.

Further in Applicant's view, the U.S. PTO has not undertaken any inquiry in connection with the third determination under Graham.
As to the level of skill in the art, applicants note the references to

Journal of Cellular Physiology 176:57-66, 1998 (Attached Reference 1).

Hematologica 2001; 86:1099-1100 (Attached Reference 2);

STEM CELLS 2003;21: 105-110 (Attached Reference 3); and

British Journal of Haematology, 2003, 121, 368-374 (Attached Reference 4)

Those references are also noted in the concurrently filed INFORMATION DISCLOSURE STATEMENT, 1449 FORM.

Applicants have provided the references relating to the level determination of skill in the art Actually, the method described in Erices *et al.* is that conventionally used in isolating mesenchymal stem cells from bone marrow. As support for this view , applicants present *Journal of Cellular Physiology* 176:57-66, 1998. That is, Erices *et al.* applied this method to obtain cells from umbilical cord blood.

However, additional information provided by applicant in the concurrently filed IDS raises the question that serious dispute as to whether this method maybe used for obtaining mesenchymal stem cells from umbilical cord blood, as clearly mentioned in *Hematologica* 2001; 86:1099-1100 (Attached Reference 2); it states as follows:

> "In the same conditions it was possible to isolate MSCs from bone marrow but not from UCB" (Abstract);
>
> "Our data did not agree with the finding of Erices *et al.* who recently identified mesenchymal progenitor cells in 25% of their UCB harvests." (in page 1099, right column)

Those 2003 references suggest that umbilical cord blood contains plenty of hematopoietic stem cells, but rarely contains mesenchymal stem cells; this is supported by *STEM CELLS* 2003;21: 105-110 (Attached Reference 3) and *British Journal of Haematology*, 2003, 121, 368-374 (Attached Reference 4), as follows:

> "Umbilical cord blood is a rich source of hematopoietic stem/progenitor cells and does not contain mesenchymal progenitors." (Abstract, Reference 3); and
>
> "Adult bone marrow is a rich source of human mesenchymal 'stem' cells but umbilical cord and mobilized adult blood are not." (Title, Reference 4)

That is, there is no evidence here that, prior to the work of applicants, any one has tried to obtain mesenchymal stem cells from umbilical cord blood. Accordingly, the record does not support the proposition that the characteristic feature of the rejected

claims (that is, mesenchymal stem cells are isolated and cultured from **umbilical cord blood**) would have been obvious to the person skilled in the art; in fact the evidence leads away from such a proposition..

Considering the above, even though Erices *et al.* discloses a method of isolating mesenchymal cells (which is used conventionally for obtaining mesenchymal stem cells from bone marrow), it does not teach or suggest the subject invention.

The secondary references do not make up for the deficiencies of Erices et al.

Nishikawa *et al.* (U. S. Patent Application Publication No.: 2004/0235160; effective filing date: Aug. 7, 2002) is directed to a process for producing hematopoietic stem cells by culturing hematopoietic stem cells in the presence of a gp130 stimulating factor, one or more cytokines and stromal cells.

Even though Nishikawa *et al.* mentions cultivation of mesenchymal stem cells (in Example 5), it never describes that these mesenchymal stem cells are obtained from umbilical cord blood. Further, even though Nishikawa *et al.* mentions collection of umbilical cord blood (in Example 6), it never describes that from the collected umbilical cord blood, mesenchymal stem cells may be obtained.

Nishikawa *et al.* discloses only a process of culturing hematopoietic stem cells, which are quite different from mesenchymal stem cells. As described above, it is well known that umbilical cord blood contains plenty of hematopoietic stem cells, but does not contains mesenchymal stem cells (see Attached References 3 and 4). Accordingly, the characteristic feature of the subject invention (that is, **mesenchymal stem cells are isolated and cultured from umbilical cord blood**) cannot be conceived from Nishikawa *et al.*, that discloses hematopoietic stem cells.

Above all, there is no motivation to combine Erices *et al.* (which relates to mesenchymal stem cells) and Nishikawa *et al.* (which relates to hematopoietic stem cells).

Petaja *et al. (J. Clin. Invest.* 99:2655-2663; 1997) relates to anticoagulant synergism of heparin and activated protein C in vitro. Petaja *et al.* discloses use of heparin of low concentration.

In claim 1 of the subject application, however, what has a volume of more than 45 ml per unit is **NOT anti-coagulant but umbilical cord blood**. That is, the "unit" does not mean anti-coagulant unit but means cord blood unit (CBU), as described in *International Journal of Laboratory Hematology*, 2008, 30, 124-132 (Attached Reference 5). Accordingly, Petaja *et al. does not* relates to the subject invention.

Considering the above, none of the cited references, alone or in combination, teaches or suggests the characteristic features of the subject invention, and moreover, no suggestion or motivation exists in the cited references.

Applicants also wish to note that the **counterpart Korean Patent Application (KR 10-2003-0079362) has been allowed to be Korean Patent Registration No. 10-0560340 (March 7, 2006).** Enclosed herewith please find a copy of the patent published in Official Gazette. In the counterpart Korean patent application, all claims have been allowed as originally filed with no limitation.

Reconsideration and an early allowance are respectfully solicited.

Respectfully submitted,

Date: July 14 , 2008

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